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<p>(21) International Application Number: PCT/EP96/04518 (22) International Filing Date: 16 October 1996 (16.10.96) (30) Priority Data: 9522615.5 3 November 1995 (03.11.95) GB (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): GIORDANI, Antonio [IT/IT]; Via Ceva, 18, I-27100 Pavia (IT). PEVARELLO, Paolo [IT/IT]; Piazza S. Pietro in Ciel d'Oro, 7/A, I-27100 Pavia (IT). SPECIALE, Carmela [IT/IT]; Via Giovanni XXIII, 21, I-20014 Nerviano (IT). VARASI, Mario [IT/IT]; Via Giambellino, 80, I-20146 Milano (IT).</p>		<p>(81) Designated States: AL, AU, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, KZ, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. With amended claims and statement.</p>
<p>(54) Title: 4-PHENYL-4-OXO-BUTANOIC ACID DERIVATIVES WITH KYNURENINE-3-HYDROXYLASE INHIBITING ACTIVITY</p> <p>(57) Abstract</p> <p>4-phenyl-4-oxo-butanoic acid derivatives for use in the treatment of the human or animal body by therapy; particularly as kynurenine-3-hydroxylase inhibitors, in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of such an enzyme is needed. The present invention further comprises a selected class of the above mentioned 4-phenyl-4-oxo-butanoic acid derivatives, their pharmaceutically acceptable salts, a process for their preparation and pharmaceutical compositions containing them.</p>		

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4-Phenyl-4-oxo-butanoic acid derivatives with kynurenine-3-
5 hydroxylase inhibiting activity.

The present invention refers to the use in the prevention and/or treatment of neurodegenerative diseases, such as, for example, Huntington's chorea, Alzheimer's disease, dementia
10 caused by aquired immunodeficiency syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma/retinopathy, infections and inflammations of the brain, of 4-phenyl-4-oxo-butanoic acid
15 derivatives which act as inhibitors of kynurenine-3-hydroxylase (KYN-3-OHase), an enzyme involved in the metabolic pathway of kynurenine.

This invention further comprises novel compounds which represent a selected class of the above mentioned 4-phenyl-4-
20 oxo-butanoic acid derivatives, their pharmaceutically acceptable salts, a process for their preparation and pharmaceutical compositions containing them.

It is well known in the art that throug the kynurenine (KYN) pathway, tryptophan metabolism gives rise to the formation of
25 quinolinic acid (QUIN) on the one side and kynurenic acid (KYNA) on the other, as shown in Figure 1.

In the last decade, several lines of evidence have demonstrated that two intermediates of the kynurenine metabolism, QUIN and KYNA, when injected in the CNS, act as a neurotoxin and as a
30 neuroprotective agent, respectively. Consequently, the demonstration that these two metabolites of the kynurenine pathway (unable to cross the blood brain barrier), are normal constituents of the mammalian brain, reveals the existence of

this pathway within the CNS and proposes the involvement of QUIN and KYNA in brain physiology and pathology (Stone T.W., Pharmacol. Rew., (1993), 310-379).

Both QUIN and KYNA are able to interact with the ionotropic
5 excitatory amino acid receptors. In particular, QUIN is a highly selective agonist at the N-methyl-D-aspartate (NMDA) receptor (Stone T.W., Eur. J. Pharmacol., 72, (1981) 411-412), whereas KYNA is a broad spectrum antagonist of the ionotropic excitatory aminoacid receptors, preferentially acting at the glycine co-
10 agonist site of the NMDA receptor (J. Neurochem., 52, (1989) 1319-1328).

In vitro studies have demonstrated that the exposure of neuronal cell cultures to relatively low QUIN concentrations are neurotoxic either when applied over a prolonged period of time
15 or in combination with glutamate (Schurr A., Brain Res., 568, (1991) 199-204). In vivo QUIN has been shown to produce convulsions and axon sparing lesions that mimic the nerve cell loss described in human neurodegenerative disorders (Schwarcz R., Science, 219, (1983) 316-318). Moreover an increase in QUIN
20 production has been demonstrated in post-ischemic gerbil brain (Saito K., J. Neurochem., 60, (1993) 180-192), following spinal cord trauma in rats (Stokes B.T., Brain Res., 633, (1994) 348-352) and in guinea pig (Blight A.R., Brain Res., 632, (1993) 314-316), and, finally, in a model of experimental allergic
25 encephalomyelitis (Flagan E.M., J.Neurochem., 64, (1995) 1192-1196).

On the other hand, KYNA has shown anticonvulsant and neuroprotective properties in several animal models (Stone T.W. Pharmacol.Rev.45, (1993) 309-379), and, additionally, the
30 experimentally-evoked rise of KYNA concentrations is capable to elicit neuroprotection and seizures reduction (Nozaki K., J. Cereb. Blood Flow Metab., (1992), 12, 400-407; Russi P., J. Neurochem., 59, (1992) 2076).

Notably, KYNA when co-injected with QUIN is able to prevent the excitotoxic neuronal damage evoked by the neurotoxin (Foster A.C., Neurosci. Lett., 48, (1984) 273-278).

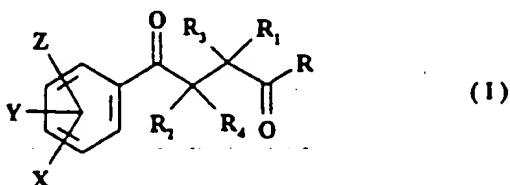
These data taken together show that KYNA may act as the brain's own defence against detrimental events, such as excitotoxicity and seizures, leading to pathological situations (Schwarcz R., Neurotoxin and neurodegenerative disease, Ann. N.Y.Sci., 140, vol. 648, 1992).

It follows that, pharmacological interventions aimed at increasing KYNA formation and/or blocking QUIN synthesis, can be useful for the therapy of excitotoxic brain diseases.

Since in the kynurenine pathway (Fig. 1) KYN-3-OHase is the first enzyme involved in the formation of QUIN from KYN, compounds which act as inhibitors of this enzyme are expected to block the metabolism toward QUIN and, at the same time, to increase KYNA formation.

Consequently, compounds able of inhibiting this enzyme are useful in the prevention and/or treatment of a variety of pathologies involving quinolinic acid or excessive activation of the neurotransmission mediated by excitatory amino acid receptors.

Accordingly, the present invention provides a 4-phenyl-4-oxo-butanoic acid derivative of formula (I) either as a single isomer or as mixture of isomers



wherein

X, Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;

R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in
5 which each R₆ is, independently, hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, phenyl or benzyl;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, C₂-C₄ alkenyl, phenyl or benzyl, or
10

R₁ and R₃ or R₂ and R₄ together form a group =CHR₈ in which R₈ is hydrogen, a straight C₁-C₅ alkyl chain or phenyl;
or a pharmaceutically acceptable salts thereof, for use in a method of treatment of the human or animal body by therapy.

15 Typically, the 4-phenyl-4-oxo-butanoic acid derivative is provided for use as a kynurenine-3-hydroxylase inhibitor.

In particular, the present invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the prevention and/or treatment of a
20 neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-hydroxylase is needed.

More in particular, this invention refers to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the prevention and/or treatment of a
25 neurodegenerative disease which comprises Huntington's chorea, Alzheimer's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis,
30 glaucoma/retinopathy, infections and inflammations of the brain.

A preferred class of compounds of formula (I) according to the invention are compounds of formula (I), if the case, either as single isomers or as a mixture of isomers, wherein

R is hydroxy or -OR₅ in which R₅ is C₁-C₆ alkyl;

one of X, Y and Z is hydrogen and the other two are, each independently, hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, phenyl, benzyl or C₂-C₄ alkenyl, or

R₁ and R₃ or R₂ and R₄ together form a group =CHR₆ in which R₆ is hydrogen, a straight C₁-C₅ alkyl chain or phenyl; and the pharmaceutically acceptable salts thereof.

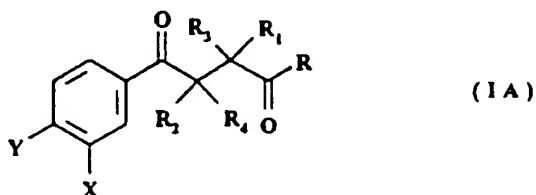
Examples of compounds of formula (I) either as single enantiomer or as mixture of enantiomers, are listed below:

- 4-(3'-chlorophenyl)-4-oxo-butanoic acid;
- 4-(3'-fluorophenyl)-4-oxo-butanoic acid;
- 4-(3'-bromophenyl)-4-oxo-butanoic acid;
- 4-(3'-nitrophenyl)-4-oxo-butanoic acid;
- 4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
- Methyl 4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
- 4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
- 4-(3'-nitro-4'-fluorophenyl)-4-oxo-butanoic acid;
- 4-(3'-nitro-4'-chlorophenyl)-4-oxo-butanoic acid;
- 4-(3'-nitro-4'-methoxyphenyl)-4-oxo-butanoic acid;
- 2-hydroxy-4-(3'-bromophenyl)-4-oxo-butanoic acid;
- 2-hydroxy-4-(3'-chlorophenyl)-4-oxo-butanoic acid;
- 2-hydroxy-4-(3'-fluorophenyl)-4-oxo-butanoic acid;
- 2-hydroxy-4-(3'-nitrophenyl)-4-oxo-butanoic acid;
- 2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
- Methyl 2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
- 2-methoxy-4-(3'-bromophenyl)-4-oxo-butanoic acid;
- 2-methoxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
- 2-methyl-4-(3'-fluorophenyl)-4-oxo-butanoic acid;
- 2-methyl-4-(3'-chlorophenyl)-4-oxo-butanoic acid;

2-methyl-4-(3'-nitrophenyl)-4-oxo-butanoic acid;
and their pharmaceutically acceptable salts.

The present invention also refers to a selected class of 4-phenyl-4-oxo-butanoic acid derivatives of formula (I), as novel
5 compounds.

The present invention therefore provide a 4-phenyl-4-oxo-butanoic acid derivative of formula (IA) either as single isomer or as a mixture of isomers



10

wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl,
15 benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in
which each of R₆ is hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄
alkynyl, phenyl or benzyl;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen,
hydroxy, cyano, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl,
20 C₂-C₄ alkenyl, phenyl or benzyl, or

R₁ and R₃ or R₂ and R₄ together form a group =CHR₈ in which R₈
is hydrogen, a straight C₁-C₅ alkyl chain or phenyl;

provided that:

- (i) when X and Y are both chlorine and R₁, R₂ and R₄ are
25 simultaneously hydrogen, R₃ is different from hydrogen,
hydroxy, methoxy, ethylthio or isopropylthio; and
(ii) when X and Y are both fluorine, R₁, R₂, R₃ and R₄ are not
simultaneously hydrogen.

This invention also comprises the pharmaceutically
30 acceptable salts of the compounds of formula (IA) as well as all

the possible isomers included in formula (IA), both separately and in mixture.

With reference to both formulae (I) and (IA), the meaning of the various substituents are as follows.

- 5 If not otherwise stated, the alkyl, alkoxy and alkylthio chains may be branched or straight chains.
- Representative examples of C_1 - C_6 alkyl chains include C_1 - C_4 alkyl chains such as methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl.
- 10 Representative examples of C_1 - C_6 alkoxy groups include C_1 - C_4 alkoxy groups such as methoxy and ethoxy.
- Representative examples of C_1 - C_6 alkylthio groups include C_1 - C_4 alkylthio groups such as methylthio, ethylthio and isopropylthio.
- 15 A halogen atom is fluoro, bromo, chloro or iodo; in particular it is fluoro or chloro.
- Representative examples of C_2 - C_4 alkenyl group include vinyl and allyl.
- Representative examples of C_2 - C_4 alkynyl include ethynyl or
- 20 propargyl.

The compounds of formula (I) or (IA) may have asymmetric carbon atoms and, for this reason, they can exist either as diastereomeric mixtures or as pure diastereoisomers. Moreover, the compounds of formula (I) and (IA), where an asymmetric

25 centre is present, can exist either as a mixture of optical isomers (enantiomeric mixture) or as single optical isomer (enantiomers).

The present invention therefore include within its scope all the possible isomers and their mixtures and, in addition, both

30 the metabolites and the pharmaceutically acceptable bioprecursors (otherwise known as pro-drugs) of the compounds of formula (I) and (IA).

The pharmaceutically acceptable salts of the compounds of formula (I) and (IA) include the salts of inorganic bases, for example hydroxides of alkali metals, e.g. sodium or potassium, or alkaline-earth metals, e.g. calcium or magnesium, and the salts of organic bases, such as, e.g., aliphatic amines, e.g. methyl amine, ethyl amine or diethyl amine, or heterocyclic amines, e.g. piperidine.

A particular class of compounds of formula (IA) according to the invention are compounds of formula (IA), if the case, either as single isomers or as mixture of isomers, wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy or -OR₅ in which R₅ is C₁-C₆ alkyl;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, cyano, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, phenyl, benzyl or C₂-C₄ alkenyl, or

R₁ and R₃ or R₂ and R₄ together form a group =CHR₆ in which R₆ is hydrogen, a straight C₁-C₆ alkyl or phenyl;

and the pharmaceutically acceptable salts thereof; provided that:

- (i) when X and Y are both chlorine and R₁, R₂ and R₄ are simultaneously hydrogen, R₃ is different from hydrogen, hydroxy, methoxy, ethylthio or isopropylthio; and
- (ii) when X and Y are both fluorine, R₁, R₂, R₃ and R₄ are not simultaneously hydrogen.

Specific examples of preferred compounds of formula (IA), either as single isomers or as mixture of isomers, are listed below:

2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;

2-methoxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;

2-hydroxy-3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-hydroxy-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

- 2-methyl-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 2-chloro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-chloro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 2-fluoro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 5 2-fluoro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 2-thiomethyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-methyliden-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 10 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 (R,S)-methyl-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
 15 (R,S)-methyl-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
 and their pharmaceutically acceptable salts.

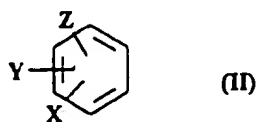
The present invention also provides a compound of formula (IA) for use in a method of treating the human or animal body by therapy.

- 20 Typically, a compound of formula (IA) is provided for use as a kynurenine-3-hydroxylase inhibitor.

The compounds of formula (I) or (IA) may be prepared by a process which comprises:

- a) reacting a compound of formula (II)

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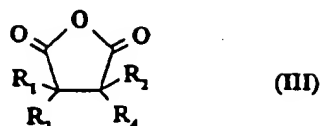


wherein

- 30 X, Y and Z are, each independently, hydrogen, halogen, cyano, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;

10

with a compound of formula (III)



5

wherein

R_1 , R_2 , R_3 and R_4 are each independently, hydrogen, C_1 - C_6 alkyl, C_2 - C_4 alkenyl, phenyl or benzyl, or

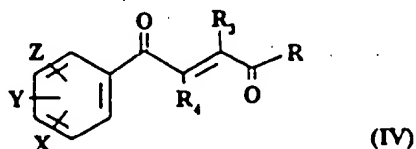
R_1 and R_3 or R_2 and R_4 together form a group $=CHR_5$ in which R_5 is hydrogen, a straight C_1 - C_5 alkyl chain or phenyl;

so obtaining a compound of formula (I) or (IA) wherein

X , Y , Z , R_1 , R_2 , R_3 and R_4 are as defined above and R is hydroxy; or

b) reacting a compound of formula (IV)

15



wherein

X , Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C_1 - C_6 alkyl, phenyl, benzyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio;

R is hydroxy or $-OR_5$ in which R_5 is C_1 - C_6 alkyl; and

R_3 and R_4 are, each independently, hydrogen, halogen, C_1 - C_6 alkyl, phenyl or benzyl;

with a compound of formula (V)



wherein

- R_1 is hydrogen, halogen, hydroxy, sulfidryl C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkyl, phenyl or benzyl; and
 R_2 is hydrogen, halogen, hydroxy, an alkali metal, e.g. lithium or an alkaline-earth metal, e.g. magnesium; provided
5 that when R_1 is sulfidryl or C_1 - C_6 alkylthio R_2 is not hydroxy or halogen;
so obtaining a compound of formula (I) or (IA) wherein
 X , Y , Z , R_1 , R_2 , R_3 and R_4 are as defined above;
and, if desired,
- 10 c) converting a compound of formula (I) or (IA) as obtained in step a) or b) above, into another compound of formula (I) or (IA) in which one or more of R_1 , R_2 , R_3 and R_4 has/have different meaning; and/or, if desired,
- d) converting a compound of formula (I) or (IA) as obtained in
15 step a), b) or c) above, into another compound of formula (I) or (IA) wherein R is not hydroxy; or, if desired,
- e) converting a compound of formula (I) or (IA) as obtained in step a), b) or c) above, into a pharmaceutically acceptable salt thereof or obtaining the free compound from the
20 corresponding salt; and/or, if the compound of formula (I) or (IA) is obtained as a mixture of isomers,
- f) obtaining a single isomer of a compound of formula (I) or (IA) as obtained in step a), b), c), d) or e) from the corresponding mixture of isomers.
- 25 The reaction of a compound of formula (II) with a compound of formula (III), described as step a), can be carried out according to known methods; for example, following the procedures reported in: Somerville L.F., Organic Synthesis, Collect. Vol. 2, 81, (1943); Child R.G., *Arzneim.-Forsch./Drug*
30 *Res.*, 30, 695-702, (1980); Quallich G.J., *J.Org.Chem.*, 55, 4971-4973 (1990); Thyges M., *J.Med.Chem.*, 26, 800-807 (1983); Hester J.B., *J.Med.Chem.*, 34, 308-315 (1991); and De Saqui-Sannes, *Pharm.Acta Helv.*, 66, 7, 189-192 (1991).

For example, this reaction can be performed in the presence of a suitable Lewis acid catalyst, in an inert solvent such as, e.g., dichloromethane or 1,2-dichloroethane, or in an appropriate aromatic hydrocarbon such as, e.g., chlorobenzene, nitrobenzene
5 or in an excess of a compound of formula (II) itself; at a temperature ranging from about -10°C to about 100°C; optionally in the presence of a co-solvent, e.g. nitromethane.

A suitable Lewis acid may be, e.g., anhydrous aluminium trichloride, anhydrous tin dichloride, titanium tetrachloride or
10 anhydrous zinc dichloride; typically, anhydrous aluminium trichloride.

The compounds of formula (II) are known compounds.

The compounds of formula (III) are known compounds or can be prepared by known procedures from known compounds.

15 The reaction of a compound of formula (IV) with a compound of formula (V), described as step b), may be carried out according to known methods: see, for example, Kazuya Kameo, Chem. Pharm. Bull., 36, 6, 2050-2060, (1988) and E. Buchia, Chem. Ber. 82, 63 (1949).

20 A compound of formula (V) may also be in the form of a salt with an alkali metal ion such as, e.g., sodium, lithium or potassium ion, preferably lithium or sodium; in this case, the compounds of formula (V) may be, e.g., sodium hydroxyde, sodium disulfide, sodium C₁-C₆ alkoxyde or sodium C₁-C₆ thiolate.

25 For example, this reaction can be carried out in an inert solvent, e.g., dioxane, tetrahydrofuran, ethyl ether, or in a solvent acting as a proton donor, e.g., water, methanol, ethanol, or in an excess of a compound of formula (V) itself, at a temperature ranging from about -50°C to the reflux
30 temperature.

A compound of formula (V) may also be in the form of an organometallic reagent, e.g., phenyl-lithium, methyl-lithium,

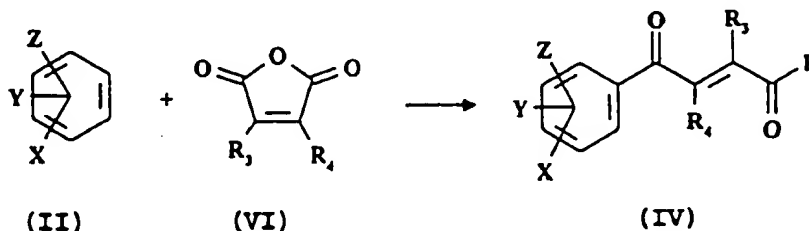
phenylmagnesium bromide or methyl magnesium bromide; in this case R_2 is, e.g., lithium or an alkaline earth-metal.

The reaction of a compound of formula (IV) with a compound of formula (V), when the compound of formula (V) is an organometallic reagent, may be carried out according to known methods; see, for example, E.Erdik, *Tetrahedron*, 40, 641-657 (1984); S.Cacchi, A.Arcadi, *J.Org.Chem.*, 48, 4236-4240 (1983); C.A.Ibarra, *J.Chem.Soc.P.T.II*, 467-470 (1991); G.Quinkert, *Angew.Chem. Int. Ed. Engl.*, 25, 992-998 (1996); J.Leonard, M.F.Jones, *Synlett*, 9, 741-742 (1992); B.Lipshutz, *Tetrahedron Lett.*, 34, 6689-6692 (1993); J.L.Leuche, *J.Org.Chem.*, 48, 3837-3846 (1983); M.Martinelli, J.Peterson, *Tetrahedron Lett.*, 31, 5401-5404 (1990); and T.Watanabe, *Synlett*, 3, 175-177 (1994). For example, this reaction can be carried out in an inert solvent, e.g., dioxane, tetrahydrofuran or ethyl ether, at a temperature ranging from about -78°C to room temperature, optionally in the presence of a transition metal catalyst.

The compounds of formula (V) are known compounds or may be prepared from known compounds according to known methods.

The compounds of formula (IV) are either known compounds or can be obtained by known methods from known compounds. For example, a compound of formula (IV) can be obtained following the process outlined in Scheme 3 below, namely, reacting a compound of formula (II) with a compound of formula (VI).

Scheme 3



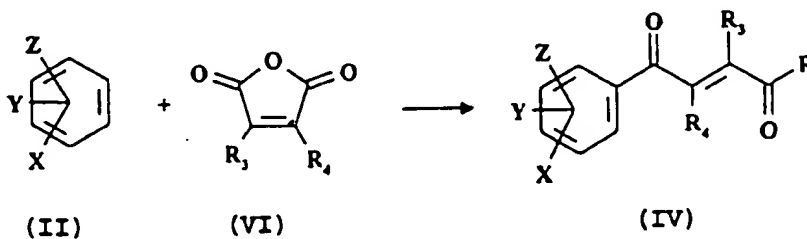
phenylmagnesium bromide or methyl magnesium bromide; in this case R_2 is, e.g., lithium or an alkaline earth-metal.

The reaction of a compound of formula (IV) with a compound of formula (V), when the compound of formula (V) is an organometallic reagent, may be carried out according to known methods; see, for example, E.Erdik, *Tetrahedron*, 40, 641-657 (1984); S.Cacchi, A.Arcadi, *J.Org.Chem.*, 48, 4236-4240 (1983); C.A.Ibarra, *J.Chem.Soc.P.T.II*, 467-470 (1991); G.Quinkert, *Angew.Chem. Int. Ed. Engl.*, 25, 992-998 (1996); J.Leonard, *M.F.Jones, Synlett*, 9, 741-742 (1992); B.Lipshutz, *Tetrahedron Lett.*, 34, 6689-6692 (1993); J.L.Leuche, *J.Org.Chem.*, 48, 3837-3846 (1983); M.Martinelli, J.Peterson, *Tetrahedron Lett.*, 31, 5401-5404 (1990); and T.Watanabe, *Synlett*, 3, 175-177 (1994). For example, this reaction can be carried out in an inert solvent, e.g., dioxane, tetrahydrofuran or ethyl ether, at a temperature ranging from about -78°C to room temperature, optionally in the presence of a transition metal catalyst.

The compounds of formula (V) are known compounds or may be prepared from known compounds according to known methods.

The compounds of formula (IV) are either known compounds or can be obtained by known methods from known compounds. For example, a compound of formula (IV) can be obtained following the process outlined in Scheme 3 below, namely, reacting a compound of formula (II) with a compound of formula (VI).

Scheme 3



In the above Scheme 3:

X, Y, and Z are, each independently, hydrogen, halogen, cyano,
C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆
5 alkoxy or C₁-C₆ alkylthio;

R₃ and R₄ are, each independently, hydrogen, C₁-C₆ alkyl, phenyl
or benzyl; and

R is hydroxy.

In a compound of formula (IV), obtained as described in Scheme
10 3, R is hydroxy, namely it contains a free carboxy group; such
a compound can be converted into another compound of formula
(IV) in which R is not hydroxy according to known methods.

The reaction of a compound of formula (II) with a compound of
formula (VI), as described in Scheme 3, can be carried out
15 according to known methods (Kazuya Kameo, Chem. Pharm. Bull., 36
(6), 2050-2060 (1988); and Bianchi M., Eur. J. Med. Chem., 23,
45-52 (1988)).

For example, the reaction can be performed in the presence of a
suitable Lewis acid catalyst, in an inert solvent such as, e.g.,
20 dichloromethane or 1,2-dichloroethane, or in a appropriate
aromatic hydrocarbon such as, e.g., chlorobenzene or
nitrobenzene, or in an excess of a compound of formula (II)
itself; at a temperature ranging from about -10°C to about
100°C; optionally in the presence of a co-solvent, e.g.
25 nitromethane.

A suitable Lewis acid may be anhydrous aluminium trichloride,
anhydrous tin dichloride, titanium tetrachloride or anhydrous
zinc dichloride; typically, anhydrous aluminium trichloride.

The compounds of formula (II) are known compounds.

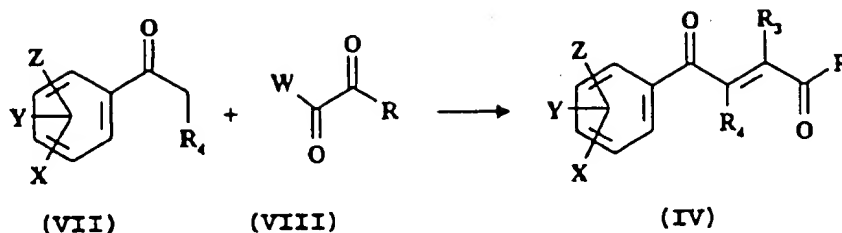
30 The compounds of formula (VI) are known compounds or can be
prepared by known procedures from known compounds.

In alternative, the compounds of formula (IV) can be
prepared following the procedure as outlined in Scheme 4 below;

namely, reacting a compound of formula (VII) with a compound of formula (VIII).

Scheme 4

5



10 In the above Scheme 4:

X, Y, and Z are as defined in Scheme 3;

R₄ is hydrogen, C₁-C₆ alkyl, phenyl or benzyl;

R₃ is hydrogen, C₁-C₆ alkyl, phenyl or benzyl;

R is hydroxy or -OR₅ in which R₅ is C₁-C₆-alkyl; and

15 W is hydrogen, hydroxy, C₁-C₆ alkyl, phenyl, benzyl or C₁-C₆ alkoxy.

A compound obtained as described in Scheme 4, containing a free carboxy group, namely a compound of formula (IV) in which R is hydroxy, can be converted into another compound of formula (IV)

20 in which R is not hydroxy according to known methods.

The reaction of a compound of formula (VII) with a compound of formula (VIII), as described in Scheme 4, can be carried out according to known methods; see, e.g., Witiak M., J. Med. Chem.,

14, 8, 758-766 (1971); Williams H.W.R., J. Med. Chem., 26, 1196-25 1200 (1983); and C.G. Wermuth, G. Leclerc, P. Melounou, Chim.Ther., 141-145 (1971).

For example, the reaction can be performed either using a suitable acid or basic catalyst, e.g., hydrochloric acid, sulfuric acid, potassium hydroxyde, sodium methoxyde or without
30 catalyst, in a solvent such as, e.g., glacial acetic acid,

dioxane, toluene or benzene, or in an excess of the compound of formula (VII) itself, at a temperature ranging from about -10°C to about 120°C.

The compounds of formula (VII) are either known compounds or
5 can be obtained from known compounds according to procedures well known in the art.

The compounds of formula (VIII) are either known compounds or can be prepared according to well known procedures.

The conversion of a compound of formula (I) or (IA) into
10 another compound of formula (I) or (IA) in which one or more of R_1 , R_2 , R_3 and R_4 has/have different meaning, described as step c), may be carried out following known procedures.

For example, a compound of formula (I) or (IA) wherein R_2 and/or R_4 are/is hydrogen can be converted into another compound of
15 formula (I) or (IA) wherein R_2 and/or R_4 substituent/s are/is C_1 - C_6 alkyl or benzyl, by means of well known procedures of ketones +alkylation, e.g. enamine or enol ethers alkylation methods, see, e.g., Carruthers, Some modern methods of organic synthesis, Cambridge University Press (1980).

20 A compound of formula (I) or (IA) wherein R_2 and/or R_4 are/is hydrogen, can be converted into another compound of formula (I) or (IA) wherein R_2 and/or R_4 are/is halogen by means of well known procedures of ketones enolates halogenation.

A compound of formula (I) or (IA) wherein R_2 and/or R_4 are/is
25 hydrogen, can be converted into another compound of formula (I) or (IA) wherein R_2 and/or R_4 are/is hydroxy by known methods, see, e.g., Hassner's α -hydroxylation of ketones, Tetrahedron Letters, 1283-86 (1981); *ibid.*, 4319-22 (1974); and *J.Org.Chem.*, 40, 3427-29 (1975).

30 A compound of formula (I) or (IA) wherein R_1 and/or R_3 are/is hydrogen and R_2 , and/or R_4 are not simultaneously hydrogen and R is $-OR_5$ in which R_5 is C_1 - C_6 alkyl, can be converted into another compound of formula (I) or (IA) wherein of the R_1 and/or R_2

are/is C₁-C₆ alkyl or benzyl, by means of well known procedures of esters enolate alkylation.

A compound of formula (I) or (IA) which contains a free carboxy group, namely a compound of formula (I) or (IA) in which
5 R is hydroxy, can be converted into another compound of formula (I) or (IA) in which R is not hydroxy.

For example, a compound of formula (I) or (IA) wherein R is hydroxy, can be converted into another compound of formula (I) or (IA) wherein R is -OR₅ in which R₅ is as defined above, by
10 usual esterification methods; for example, following the procedure described in: E. Haslam, Tetrahedron, 36, 2409-2433 (1980). Preferably, such an esterification reaction can be carried out via a reactive intermediate of the carboxylic acid, which may be isolated or not, by reaction with the appropriate
15 alcohol of formula R₅OH in which R₅ is as defined above. The reaction can be carried out in a customary solvent, e.g. dichloromethane, tetrahydrofuran, toluene, or in the presence of an excess of the alcohol itself of formula R₅OH, at a temperature which may range from about -20°C to about 50°C.
20 Intermediate reactive derivatives of the carboxylic acid may be, for example, acid halides, e.g. chloride, mixed anhydrides, e.g. etoxycarbonyl or tert-butyloxy anhydride, or a suitable reactive intermediate obtained "in situ", for example, by reaction with, e.g., dicyclohexylcarbodiimide or carbonyl diimidazole.

25 The esterification reaction may be also carried out by treatment of a compound of formula (I) or (IA) in which R is hydroxy, with a suitable alkylating agent of formula R₅-X in which R₅ is as defined above, and X is an appropriate leaving group such as, e.g., a halogen atom, preferably iodine, or a sulfate ester, in
30 the presence of an inorganic base, e.g. potassium carbonate or bicarbonate, or in the presence of an organic base, e.g. diazabicycloundecene (DBU), in a suitable solvent, e.g.

dimethylformamide, at a reaction temperature that may range from about 0°C to about 60°C.

Furthermore, a compound of formula (I) or (IA) wherein R is hydroxy, can be converted into a corresponding compound of formula (I) or (IA) wherein R is $-N(R_g)_2$ or $-NOR_g$, wherein R_g is as defined above, according to known methods; preferably, via an intermediate reactive derivative thereof, which can be isolated or not. Intermediate derivatives may be active esters, e.g., NO_2 -phenyl esters or N-hydroxysuccinimide esters, acid halides, preferably chlorides, mixed anhydrides, e.g. ethoxycarbonyl or tert-butyloxycarbonyl anhydrides, or reactive intermediates obtained "in situ" by reaction of the acid with carbonyl diimidazole.

For example, a reactive intermediate as defined above, which can be obtained following conventional ways (for example, those usually employed in the synthesis of peptides), is reacted with ammonia or an appropriate amine $HN(R_g)_2$, or an appropriate hydroxylamine or protected hydroxylamine of formula $HNO-R$, wherein R_g is a suitable C_1 - C_6 alkyl or benzyl substituent or protecting group; in this last case, R_g is preferably a benzyl or trialkyl-silyl group. The reaction solvent may be a customary solvent, such as e.g., dichloromethane, tetrahydrofuran, dioxane or an excess of the amine itself, and the reaction temperature may range from about -20°C to about 50°C.

The carbonyl group present in the compound of formula (I) or (IA) may be optionally protected during the above described reactions of transformation of a compound of formula (I) or (IA) into another compound of formula (I) or (IA). The carbonyl protection may be carried out using the techniques of carbonyl protection well known in the art, e.g., H.Meerwein, in: Houben-Weyl, Methoden der Organischen Chemie, Vol.VI/4, George Thieme Verlag, p.222 (1965). The removal of the carbonyl protecting group at the end of the transformation may be carried out with

usual methods, e.g., M.E.Jung, Tetrahedron Lett., 48, 4175-4178 (1977); R.Sterzycki, Synthesis, 24-725 (1979); G.Baleme, 48, 3336-3338 (1983); and B.H.Lipshutz, Synthetic communications, 12, 267-277 (1982).

5 The optional salification of a compound of formula (I) or (IA) as well as the conversion of a salt into the corresponding free compound and the separation of a mixture of isomers into the single isomer, may be carried out by usual methods. For example, the separation of a mixture of regioisomers or diastereoisomers into the single isomer may be carried out by
10 conventional methods. Particularly, the separation of regioisomers or diastereoisomers may be carried out by fractional crystallization from a suitable solvent or by chromatography, either flash column chromatography or high
15 pressure liquid chromatography.

As previously described, some of the compounds of formula (I) or (IA) may exist as enantiomers; where enantiomers of compounds of formula (I) or (IA) are possible, the separation of the racemic compounds of formula (I) or (IA) into the
20 corresponding pure enantiomers can be carried out according to techniques and procedures well known in the art; for example, either high pressure liquid chromatography on a chiral stationary phase, or resolution via diastereoisomeric salt formation of a compound of formula (I) or (IA) where R is
25 hydroxy, with a suitable optically active organic base, e.g. phenylethylamine, ephedrine or brucine, and subsequent separation of the pure diastereoisomeric salt by selective recrystallization.

As already said, the compounds of formula (IA) represent a
30 selected class of compounds of formula (I) and are thus effective in the prevention and/or treatment of all the disease for which the compounds of formula (I) have been indicated as therapeutic agents.

Accordingly, the compounds of formula (IA) are useful as kynurenine-3-hydroxylase inhibitors; in particular, they are useful in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-hydroxylase is needed.

More in particular, the compounds of formula (IA) can be useful in the prevention and/or treatment of a neurodegenerative disease which comprises: Huntington's chorea, Alzheimer's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma/retinopathy, infections and inflammation of the brain.

A human or animal may thus be treated by a method which comprises the administration of a pharmaceutically effective amount of a compound of formula (I) or (IA) or salt thereof.

The efficacy of the compounds of formula (I) or (IA) in the inhibition of the enzyme kynurenine-3-hydroxylase has been evaluated both in rat brain homogenate and in rat liver homogenate, determining the conversion of L-kynurenine to L-3-hydroxy-kynurenine according to the methods described below.

Kynurenine-3-hydroxylase assay in the rat brain

Brain was homogenized in ice-cold 0.32 M sucrose and centrifuged at 12000 x g for 30 min at 4°C. The pellet was washed three times with 0.32 M sucrose by centrifugation and suspended in 0.14 M KCl in 20 mM K-phosphate buffer at pH 7 (1 g tissue in 2 ml buffer).

The reaction mixture contained: 75 µl of suspended homogenate; 100µl of substrate solution containing 50 mM K-phosphate buffer pH 7.5, 2 mM MgCl₂, 0.4 mM NADPH, 50 µM L-kynurenine (final concentration), and 25 µl of different concentrations of inhibitor solutions. The reaction was stopped by addition of 200 µl of 1 M HClO₄ after 60 min incubation. L-3-hydroxykynurenine

formed was quantified by HPLC with coulometric detection at a working voltage of +0.2 V. The column was a 10 cm C₁₈ reversed phase (3 μ m. The mobile phase consisted of 950 ml distilled water, 20 ml acetonitrile, 9 ml triethylamine, 5.9 ml phosphoric acid, 100 mg sodium EDTA and 1.5 g heptanesulfonic acid. The flow rate was 1 ml/min.

Kynurenine-3-hydroxylase assay in the rat liver

The efficacy of the compounds of the present invention in the inhibition of the enzyme kynurenine-3-hydroxylase has been evaluated in rat liver mitochondrial extract as reported below, according to known methods (A Radiometric Assay for Kynurenine 3-Hydroxylase Based on the Release of ³H₂O during Hydroxylation of L-(3,5-³H)Kynurenine; Joel B.Erickson, Ellen M.Flanagan, Suzanne Russo, and John F.Reinhard.Jr.; Analytical Biochem. (1992), 205, 257-262) with minor modifications.

The assay for kynurenine 3-hydroxylase was based on the enzymatic synthesis of tritiated water during the hydroxylation reaction. Radiolabeled water was quantified following selective adsorption of the isotopic substrate and its metabolite with activated charcoal.

Rat liver mitochondrial extract was used as enzymatic preparation for this assay.

The assay for kynurenine 3-hydroxylase activity was carried out at 37°C for a time of 30 min. The reaction mixture of a total volume of 100 μ l was constituted of 44 μ g of suspended extract, 100 mM Tris/Cl⁻ buffer pH 8.1, 10 mM EDTA, 100 mM KCl, 0.8 mM NADPH, 0.025 mM L-kynurenine, 0.5 mCi L-(3,5-³H)Kynurenine (10 Ci/mmol) and 10 μ l of different concentration of inhibitor solutions. After the incubation the reaction was terminated by the addition of 1 mL of 7.5% (w/v) activated charcoal, vortexed and centrifugated for 7 min.

A 500 μ l aliquot of supernatant was counted by scintillation spectroscopy in 5 mL of liquid scintillation.

As an example, the compounds of the present invention:

- 4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid, (internal code:
PNU 156588);
- 4-(3',4'-difluorophenyl)-4-oxo-butanoic acid (internal code: PNU
5 157720);
- Methyl 4-(3',4'-dichlorophenyl)-4-oxo-butanoate (internal code:
PNU 158381);
- (R,S)-2-hydroxy-4-(3'-chlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 158789);
- 10 (R,S)-2-hydroxy-4-(3'-fluorophenyl)-4-oxo-butanoic acid
(internal code: PNU 158790);
- (R,S)-2-hydroxy-4-(3'-nitrophenyl)-4-oxo-butanoic acid (internal
code: PNU 158791);
- (R,S)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
15 (internal code: PNU 157695)
- (S)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 161176);
- (R)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 161210);
- 20 Methyl (R,S)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoate
(internal code: PNU 161211)
- (R,S)-2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid
(internal code: PNU 158783);
- (R,S)-2-methoxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid
25 (internal code: PNU 158380);
- (R,S)-2-methoxy-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid
(internal code: PNU 157960);
- (R,S)-2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 157718);
- 30 (R,S)-3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 161243);
- 2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(PNU 167536);

- (R,S)-2-methyl-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid
(internal code: PNU 157952);
- (R,S)-2-chloro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 158781);
- 5 2-methyliden-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 158432);
- (R,S)-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 167541);
- (R,S)-Methyl-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoate
10 (internal code: PNU 167531);
- (R,S)-2-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic
acid(internal code: PNU 167533); and
- (R,S)-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
(internal code: PNU 167532);
- 15 have been tested according to the methods described above.
The obtained results, are reported in the following Table 1.

Table 1

Compound	IC ₅₀ (μM) (Brain)	IC ₅₀ (μM) (Liver)
PNU 156588	0.9	3.9
PNU 157720	3.7	18.3
PNU 158381	-	5.7
PNU 158789	0.45	1.8
PNU 158790	5.6	11.5
PNU 158791	1.95	11.2
PNU 157695	0.3	1.4
PNU 161176	0.28	0.42
PNU 161210	6.7	14.4
PNU 161211	3.1	5.6
PNU 158783	1.45	2.8
PNU 158380	12.6	42.4
PNU 157960	1.2	6.9
PNU 157718	3.5	6.9
PNU 161243	14.3	-
PNU 167536	-	61.6
PNU 157952	3.9	55.1
PNU 158781	2.2	13.3
PNU 158432	-	36
PNU 167541	-	55.0
PNU 167531	-	1.9
PNU 167533	-	19.5
PNU 167532	-	0.8

The tested compounds were found to be significantly active
5 in inhibiting the enzyme kynurenine-3-hydroxylase.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or

suspensions; parenterally, e.g. intramuscularly or by intravenous injection or infusion.

The dosage level suitable for administration to adult humans depends on the age, weight, conditions of the patient and on the administration route; for example, the dosage adopted for oral
5 administration for the compounds of the invention may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.

The present invention also provides pharmaceutical compositions comprising a compound of formula (I) or (IA) as an
10 active ingredient in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

Furthermore, the present invention provides pharmaceutical compositions comprising a compound of formula (I) as an active ingredient in association with a pharmaceutically acceptable
15 excipient (which can be a carrier or a diluent) for use as kynurenine 3-hydroxylase inhibitor.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable
20 form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate,
25 and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as
30 lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of

mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

- 5 The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

- 10 The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous
15 injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The following examples illustrate but do not limit the invention.

20

Example 1

(R,S)-2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid (PNU 157718)

- Aluminium chloride anhydrous (2g, 53 mmol.) was added to a
25 solution of (R,S)-2-methylsuccinic anhydride (2 g, 17 mmol) in dichlorobenzene (16 g, 100 mmol) at ambient temperature. The reaction mixture was heated to 60°C for 3 hours. and then inverse quenched onto cold water (160 ml), maintaining the temperature below 50°C. After stirring for 15 min., hexane (80
30 ml) was added and stirring continued for 1.5 hours. The product was filtered and dried in a vacuum oven to give the crude ketoacid as a slightly brown solid, 4.4 g (mp. 98-101°C).

The above crude reaction product was recrystallized from diisopropyl ether to provide 3.5 g (76%) of the pure acid (mp. 119-120°C), colorless solid.

Calcd. for $C_{11}H_{10}Cl_2O_3$: C 50.60 ; H 3.86 ; Cl 27.20

5 Found : 48.97 ; 3.94 ; 26.68

MS, EI : 260.0 (M)⁺; 173 ($C_6H_3Cl_2CO$)⁺.

¹H NMR (200 MHz; d_6 -DMSO), ppm : 1.18 (3H, d); 2.85 (1H, m); 3.08 (1H, dd); 3.40 (1H, dd); 7.78 (1H, d); 7.92 (1H, dd); 8.14 (1H, d).

10

Analogously, the following compound can be prepared:

2-methyl-4-oxo-4-(3',4'-difluorophenyl)butanoic acid (PNU 157952), colorless needles, mp. 83-85°C

15 Calcd. for $C_{11}H_{10}F_2O_3$: C 57.89 ; H 4.42 ;

Found : 57.78 ; 4.61 ;

¹H NMR (200 MHz; d_6 -DMSO), ppm : 1.18 (3H d); 2.83 (1H, m); 3.10 (1H, dd); 3.40 (1H, dd); 7.30-7.65 (1H, m); 7.80-7.90 (1H, m); 7.96-8.08 (1H, m); 12.20 (1H, s).

20

Analogously, using 2-acetoxysuccinic anhydride, the following compounds can be prepared:

(R,S)-2-hydroxy-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 157695); colorless needles, mp. 150-151°C.

Calcd. for $C_{10}H_8Cl_2O_4$: C 45.67 ; H 3.07 ; Cl 26.99

Found : 45.41 ; 3.16 ; 27.14

MS (EI)m/z: 262 (M)⁺; 243.9 (M-H₂O)⁺; 217.0 (M-COOH)⁺; 173 ($C_6H_3Cl_2CO$)⁺.

30 ¹H NMR (200 MHz; d_6 -DMSO), ppm : 3.36 (2H, d); 4.42 (1H, t); 7.76 (1H, d); 7.92 (1H, dd); 8.12 (1H, d); 12.20 (1H, bs);

(S)-2-hydroxy-4-oxo-(3',4'-dichlorophenyl)butanoic acid (PNU 161176); analogously obtained in 55% yield, using homochiral (S)-2-acetoxysuccinic anhydride: colorless needles, mp. 148-19.5°C,

5 $[\alpha]_D = -8.55^\circ$ (EtOH Abs.; c = 0.99).

Calcd. for $C_{10}H_8Cl_2O_4$: C 45.67 ; H 3.07 ; Cl 26.99

Found : 45.87 ; 3.23 ; 26.25; and

(R)-2-hydroxy-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 161210); analogously obtained in 58% yield, using homochiral (R)-2-acetoxysuccinic anhydride: colorless needles, mp. 150-152°C,

$[\alpha]_D = +8.04^\circ$ (EtOH Abs.; c = 0.97).

Calcd. for $C_{10}H_8Cl_2O_4$: C 45.67 ; H 3.07 ; Cl 26.99

15 Found : 45.73 ; 3.14 ; 27.03.

Analogously, using succinic anhydride, the following compounds can be prepared:

20 4-oxo-4-(3',4'-difluorophenyl)butanoic acid (PNU 157720), m.p. 80-81°C;

Calcd. for $C_{10}H_8F_2O_3$: C 56.10 ; H 3.32

Found : 56.32 ; 3.72

25 MS (EI) m/z: 214.0 (M)⁺; 141.0 (C₆H₃F₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 2.58 (2H, t); 3.21 (2H, t);

7.53-7.66 (1H, m); 7.82-8.04 (2H, m); 12.10 (1H, s); and

4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 156588), m.p. 166-167°C.

30 Calcd. for $C_{10}H_8Cl_2O_3$: C 48.63 ; H 3.26 ; Cl 28.74

Found : 48.59 ; 3.31 ; 28.35

MS (FAB⁺) m/z: 245 (M-H)⁺.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 2.57 (2H, t); 3.23 (2H, t); 7.79 (1H, d); 7.92 (1H, dd); 8.18 (1H, s); 12.10 (1H, broad s).

- 5 Analogously, using 2,2-dimethylsuccinic anhydride, the following compound can be prepared:

2,2-dimethyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid: light cream plates, m.p. 137-138°C (diisopropyl ether),

10 Calcd. for $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{O}_3$: C 52.39 ; H 4.40 ; Cl 25.77
Found : 52.95 ; 4.63 ; 25.22

MS (EI) m/z : 274 (M) $^{+}$; 188 ($\text{C}_6\text{H}_3\text{Cl}_2\text{COCH}_3$) $^{+}$; 173 ($\text{C}_6\text{H}_3\text{Cl}_2\text{CO}$) $^{+}$.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 1.20 (6H, s); 3.35 (2H, s); 7.78 (1H, d); 7.90 (1H, dd); 8.16 (1H, s); 12.0 (1H, s).

15

Example 2

2-methyliden-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 158432)

- 20 Aluminium chloride anhydrous (53 g, 0.13 mol.) was added to a solution of itaconic anhydride (15 g, 0.13 mol.) in dichlorobenzene (100 mL) at room temperature. The reaction mixture was heated to 50°C for 3 hours. and then inverse quenched with cold water/ 37% hydrochloric acid (100 mL/100 mL)
- 25 maintaining the temperature below 30°C. After stirring the quenched reaction for 15 min., hexane (80 mL) was added and stirring continued for 0.5 hours. The product was filtered and dried in a vacuum oven to give the crude unsaturated-ketoacid as a colourless solid, 36 g, recrystallization from diethyl ether
- 30 provided the pure acid (22 g, 67%) as colourless prisms melting at 156-57°C.

Calcd. for $\text{C}_{11}\text{H}_8\text{Cl}_2\text{O}_3$: C 51.01 ; H 3.11 ; Cl 27.41
Found : 51.00 ; 3.18 ; 27.00

MS (EI) m/z: 258 (M)⁺; 173 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 4.12 (2H s); 5.68 (1H, s); 6.12 (1H, s); 7.80 (1H, d); 7.96 (1H, dd); 8.18 (1H, d); 12.50 (1H, s).

5 Example 3

(R,S)-2-methoxy-4-oxo-4-(3',4'-difluorophenyl) butanoic acid
(PNU 158380).

4-oxo-4-(3',4'-difluorophenyl)-2-butenic acid (RN: 83844-24-0) was prepared according to Scheme 3 in 55% yield; yellow solid
10 melting at 107-108°C (toluene), ¹H-NMR (d₆-DMSO) ppm: 6.65 (d, 1H); 7.55-7.64 (m, 1H); 7.83 (d, 1H); 7.85-8.11 (m, 2H); 13.1 (broad s, 1H).

To a solution of 4-oxo-4-(3',4'-difluorophenyl)-2-butenic acid (3 g, 14.1 mmol) in dry methanol (300 mL), cooled at 0°C,
15 under dry nitrogen atmosphere, sodium methoxide (1.9 g, 35.2 mmol) dissolved in dry methanol (50 mL), was slowly added, on vigorous stirring and maintaining the temperature below 5°C. The resulting solution was stirred at 0°C for one hour, then quenched with glacial acetic acid (1 mL) and evaporated in
20 vacuo. The residue was taken up with ethyl acetate (100 mL), washed with 1N HCl (3 x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated in vacuo to provide 3.2 g of crude product as colorless oily material.

Column flash chromatography (SiO₂; CH₂Cl₂/ MeOH 98:2) afforded
25 the pure acid (2.1 g, 62%); colorless prisms melting at 65-66°C.

Calcd. for C₁₁H₁₀F₂O₄ : C 54.15 ; H 4.13

found : C 53.19 ; H 4.33

MS, EI (m/z) : 226.1 (M)⁺; 141.1 (C₆H₃F₂CO)⁺.

30 ¹H NMR (200 MHz; d₆-DMSO), ppm : 3.25 (s, 3H); 3.23-3.45 (m, 2H); 4.18 (t, 1H); 7.45-7.60 (m, 1H); 7.80-8.0 (m, 2H); 12.8 (broad s, 1H).

Analogously, using sodium hydroxide instead of sodium methoxyde, the following compound can be prepared:

(R,S)-2-hydroxy-4-oxo-4-(3',4'-difluorophenyl)butanoic acid (PNU
5 158783) m.p. 111-112°C.

Calcd. for $C_{10}H_8F_2O_4$: C 52.18 ; H 3.50

found : C 52.34 ; H 3.58

MS, FAB⁺ (m/z) : 231.5 (M+H)⁺; 214.6; 141.3.

MS, FAB⁻ (m/z) : 229.6 (M+H)⁻; 211.3 (M-H₂O-H)⁻.

10 ¹H NMR (200 MHz; d₆-DMSO), ppm : 3.23 (d, 2H); 4.42 (t, 1H);
7.58 (m, 1H); 7.82 (m, 1H); 7.98 (m, 1H); 12.8 (broad s, 1H).

Analogously, using sodium sulfide or sodium methylthiolate, the following compound can be prepared:

15

(R,S)-2-thio-4-oxo-4-(3',4'-difluorophenyl)butanoic acid.

(R,S)-2-thiomethyl-4-oxo-4-(3',4'-difluorophenyl)butanoic acid.

Analogously, using sodium methoxide, 2-methoxy-4-oxo-4-(3',4'-
20 dichlorophenyl)butanoic acid (PNU 157960), colorless needles,
m.p. 98°-99°C,

Calcd. for $C_{11}H_{10}Cl_2O_4$: C 47.70 ; H 3.64 ; Cl 25.63

Found : 47.84 ; 3.68 ; 25.79

MS (EI) m/z: 276 (M)⁺; 258 (M-H₂O)⁺; 173 (C₆H₃Cl₂CO)⁺.

25 ¹H NMR (200 MHz; d₆-DMSO), ppm : 3.27 (3H, s); 3.38 (2H, m); 4.18
(1H, m); 7.76 (1H, d); 7.91 (1H, dd); 8.13 (1H, d); 12.80 (1H,
broad s)

was prepared starting from 4-oxo-4-(3',4'-dichlorophenyl)-2-
butenoic acid (RN: 22660-10-2), which was in turn prepared
30 according to Scheme 3 in 87% yield; yellow needles melting at
146-147°C (toluene).

Analogously, using sodium hydroxide instead of sodium methoxyde, the following compound can be prepared:

- (R,S)-2-hydroxy-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid:
5 (PNU 157695), colorless prisms, mp.150-151°C.
Calcd. for C₁₀H₈Cl₂O₄ : C 45.67 ; H 3.07 ; Cl 26.99
Found : 45.41 ; 3.16 ; 27.14
MS (FAB) m/z: 263.3 (M+H)⁺.
¹H NMR (200 MHz; d₆-DMSO), ppm : 3.32 (2H, d); 4.43 (1H, t);
10 7.78 (1H,d); 7.93 (1H,dd); 8.18 (1H,d); 12.80 (1H, broad s).

Analogously, using sodium sulfide or sodium methylthiolate, the following compounds can be prepared:

- 15 (R,S)-2-thio-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid; and
(R,S)-2-thiomethyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid.

Example 4

- (R,S)-2-chloro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid (PNU
20 158781)).

A solution of 4-oxo-4-(3',4'-dichlorophenyl)-2-butenic acid (RN: 22660-10-2) (3.2 g, 13.1 mmol) in glacial acetic acid (320 mL), was saturated with dry HCl at 0°C, on stirring.

- The resulting solution was heated at 70°C over 6 hours, during
25 this time anhydrous hydrochloric acid was slowly bubbled through the solution. The reaction mixture was then evaporated in vacuo and the residue coevaporated from toluene. The resulting oily material was dissolved in diethyl ether and extracted with saturated sodium bicarbonate solution. The aqueous phase was
30 washed with ether and the pH adjusted to 2 by addition of 37% HCl, the precipitated crude product was filtered, washed with water and dried. Recrystallization from toluene provided the pure acid as colorless solid, mp. 146-147°C.

^1H NMR (d_6 -DMSO) ppm: 3.80 (m, 2H); 4.78 (t, 1H); 7.83 (d, 1H); 7.94 (dd, 1H); 8.18 (d, 1H); 13.1 (broad s, 1H):

MS (FAB) m/z : 281.1 (M-H) $^-$; 243.1 (M-HCl-H) $^-$.

Calcd. for $\text{C}_{10}\text{H}_7\text{Cl}_3\text{O}_3$: C 42.66; H 2.51; Cl 37.78

5 found: C 43.04; H 2.60; Cl 37.26

Analogously, starting from 4-oxo-4-(3',4'-difluorophenyl)-2-butenic acid, the following compound can be obtained:

10 (R,S)-2-chloro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid.

Analogously, using hydrofluoric acid instead of hydrochloric acid the following compounds can be obtained:

15 (R,S)-2-fluoro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid; and
(R,S)-2-fluoro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid.

Example 5

(R,S)-Methyl-4-oxo-4-(3',4'-dichlorophenyl) butanoate (PNU

20 158381).

To a solution of 4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (6g, 27 mmol) in methanol (250 mL), 6N HCl methanolic solution (25 mL) was added at room temperature. The resulting solution was refluxed for 3 hours, then evaporated in vacuo. The obtained
25 oily residue was dissolved in hexane/ diisopropyl ether (80:20) on heating at reflux, the resulting solution was filtered, and cooled at room temperature. On standing at +5°C the pure ester precipitated as colorless prisms (6.2 g, 88%), mp. 74-75°C.

30 Calcd. for $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{O}_3$: C 50.62; H 3.86; Cl 27.20
found: 51.57; 3.87; 26.97

MS, EI (m/z): 260.0 (M) $^+$; 173.0 ($\text{C}_6\text{H}_3\text{Cl}_2\text{CO}$) $^+$.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 2.63 (2H, t); 3.32 (2H, t); 3.60 (3H, s); 7.80 (2H, d); 7.94 (1H, dd); 8.18 (1H, d).

Example 6

5 (R,S)-Methyl-2-hydroxy-4-oxo-(3',4'-dichlorophenyl)butanoate
(PNU 161211)

To a solution of (R,S)-Methyl-2-hydroxy-4-oxo-(3',4'-dichlorophenyl)butanoate (2.63 g, 10 mmol) in dry DMF (50 mL), under dry nitrogen atmosphere, DBU (2.7 mL, 18 mmol) was added
10 on stirring at 0°C, followed by dropwise addition of iodomethane (6.2 mL, 0.1 mol). The resulting deep red solution was stirred at 0°C over 2 hours, further stirring at room temperature an additional hour completed the reaction. The resulting mixture was poured into 0.5 N aqueous HCl/ice (1:1, w/w) and extracted
15 with diethyl ether, the combined organic layers were washed with water, saturated bicarbonate solution, brine and dried (Na_2SO_4). Concentration of the solvent in vacuo, afforded an oily residue which crystallized on treatment with hexane/diisopropyl ether, to provide the pure ester (2.54 g, 91%), mp. 71-72°C.

20 Calcd. for $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{O}_4$: C 47.69 ; H 3.64 ; Cl 25.60
found : 47.76 ; H 3.76 ; 25.37

MS, FAB⁺ (m/z) : 277.1 (M)⁺.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 3.38 (2H, d); 3.61 (3H, s); 4.53 (1H, q); 5.72 (1H, d); 7.78 (1H, d); 7.84 (1H, dd);
25 8.18 (1H, d).

Example 7

(R,S)-2-hydroxy-4-oxo-4-(3'-chlorophenyl)butanoic acid (PNU
158789)

30 A well stirred mixture of 3-chloroacetophenone (18.9 g, 0.1 mol) and glyoxylic acid monohydrate (9.2 g, 0.1 mol) was heated at 60°C under vacuum (25 mmHg), over 16 hours. The residue was taken up with diethyl ether and the organic phase was extracted

with saturated NaHCO_3 solution, the combined aqueous layers were washed with ether, cooled at 0°C and the pH of the solution was adjusted to 2 by addition of 37% HCl . The resulting suspension was extracted with ethyl acetate, and the combined organic
5 extracts washed with water, dried (Na_2SO_4) and concentrated in vacuo to provide the crude product. Column chromatography (SiO_2 ; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) afforded the pure titled compound as colorless needles, mp. $98-100^\circ\text{C}$ (Diisopropyl ether/pentane).

Calcd. for $\text{C}_{10}\text{H}_9\text{ClO}_4$: C 52.56; H 3.97 ; Cl 15.56

10 found : 52.35; H 3.88 ; Cl 15.16

MS , FAB^+ (m/z) : 229.3 (M) $^+$.

MS , FAB^- (m/z) : 227.1 (M- H) $^-$; 209.1 (M- H_2O -H) $^-$.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 3.32 (2H , d); 4.42 (1H, t);
7.53 (1H, t); 7.72 (1H, dd); 7.91 (m, 2H); 12.80 (broad s, 1H).

15

Analogously, starting from the appropriate acetophenones, the following compounds can be obtained:

(R,S)-2-hydroxy-4-oxo-4-(3'-fluorophenyl)butanoic acid (PNU
20 158790): colorless prisms, mp. $96-98^\circ\text{C}$ (diethyl ether/hexane).

Calcd. for $\text{C}_{10}\text{H}_9\text{FO}_4$: C 56.65 ; H 4.28

found : 56.51 ; H 4.34

MS , FAB^+ (m/z) : 213.4 (M) $^+$.

MS , FAB^- (m/z) : 211.2 (M) $^-$; 193.1 (M- H_2O -H) $^-$.

25 ^1H NMR (200 MHz; d_6 -DMSO), ppm : 3.35 (2H , d); 4.43 (1H, t);
7.40-7.82 (4H , m); 12.60 (broad s, 1H); and

(R,S)-2-hydroxy-4-oxo-4-(3'-nitrophenyl)butanoic acid (PNU
158791): colorless solid, mp. $139-140^\circ\text{C}$.

30 Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_6$: C 50.26 ; H 3.80 ; N 5.86

found : 50.26 ; 3.93 ; 5.77

MS (FAB^-) m/z: 238.2 (M-H) $^-$; 220.2 (M- H_2O -H) $^-$.

¹H NMR (200 MHz; d₆-DMSO), ppm : 3.40 (2H, d); 4.53 (1H, t); 7.80 (1H, t); 8.34-8.46 (2H, m); 8.61 (1H, d); 12.30-12.60 (broad s, 1H).

5 **Example 8**

2-hydroxy-3-methyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid
(PNU 161244).

To a solution of 1-(3,4-dichlorophenyl)propanone (5.8 g, 28.5 mmol) in 95% ethanol (100 mL) a solution of glyoxylic acid monohydrate (2.63 g, 28.5 mmol) in water (20 mL) was added at 10 0°C, followed by dropwise addition of a solution of sodium hydroxide (4.6 g, 0.114 mol). The temperature during the addition was maintained below +5°C on cooling. The resulting reaction mixture was stirred at 0°C over 3 hours, then allowed 15 to warm to room temperature and stirred further 12 hours. The most of ethanol was then removed under reduced pressure (15°C), the residue was diluted with water and the pH of the obtained suspension adjusted to 2 by addition of 37% HCl, on stirring and cooling at 0°C. The aqueous phase was extracted with ethyl 20 acetate, and the collected organic extracts were washed with brine, dried and evaporated to provide the crude reaction product as a light yellow oil (4.4 g). Column chromatography (SiO₂; CH₂Cl₂/MeOH 95:5) provided the pure titled compound (2.1 g, 27%), colorless solid (Ethyl ether/hexane) mp. 103-104°C;

25. Calcd. for C₁₁H₁₀Cl₂O₄ : C 47.40 ; H 3.64; Cl 25.60
found : 47.86 ; H 3.73; Cl 25.64
MS, EI (m/z) : 280.0 (M)⁺; 257.9 (M-H₂O)⁺; 231.0 (M-COOH)⁺;
172.9 (C₆H₃Cl₂CO)⁺.
¹H NMR (200 MHz; d₆-DMSO), ppm : 1.08 (3H, d); 3.81 (1H, q);
30 4.18 (1H, d); 7.80-7.91 (2H, m); 8.09 (1H, d).

Analogously, starting from the appropriate ketones, the following compound can be obtained:

2-hydroxy-3-benzyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 167536): obtained from 1-(3',4'-dichlorophenyl)-3-phenyl propanone, colorless prisms, mp. 131-133°C.

5 Calcd. for $C_{17}H_{14}Cl_2O_4$: C 57.83 ; H 4.00 ; Cl 20.08
found : 58.17 ; H 3.87 ; Cl 19.38

1H NMR (200 MHz; d_6 -DMSO), ppm : 3.22 (2H, m); 4.11 (1H, m); 4.29 (1H, d); 7.18-7.30 (5H, m); 7.48 (1H, d); 7.62 (1H, dd). 7.89 (1H, d).

10

2-hydroxy-3-phenyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid can be analogously prepared starting from 1-(3',4'-dichlorophenyl)-2-phenyl ethanone.

Example 9

15 4-(3'-nitrophenyl)-4-oxo-butanoic acid (PNU 157957)

To a suspension of triacetoxyborohydride (Aldrich) (21 g, 10 mmol) in dry THF (220 mL), a solution in dry THF (40 mL) of 4-(3'-nitrophenyl)-4-oxo-2-butenic acid (2.2 g, 10 mmol) (prepared as described in example 7, (mp. 178-179°C)), was added on stirring at room temperature, under dry nitrogen atmosphere. The resulting light yellow solution was stirred at room temperature overnight under nitrogen atmosphere. To the colorless reaction mixture, aqueous 1N HCl (50 mL), was slowly added dropwise, on cooling at 0°C. The most of the solvent was evaporated under reduced pressure and the residue taken up with 2N HCl and extracted with the ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated in vacuo, to lead to a solid. Recrystallization from diethyl ether/hexane afforded a cream solid (1.7g, 77%), mp. 162-164°C.

25 30 Calcd. for $C_{10}H_9NO_6$: C 53.81 ; H 4.06 ; N 6.27
found : 54.26 ; 4.18 ; 5.97

MS (FAB⁺) m/z: 222 (M-H)⁺.

^1H NMR (200 MHz; d_6 -DMSO), ppm : : 2.63 (2H, t); 3.32 (2H, t); 7.80 (1H, t); 8.34-8.46 (2H, m); 8.61 (1H, d); 12.30-12.60 (broad s, 1H).

- 5 Analogously, the following compounds may be obtained starting from the appropriate compounds of formula (IV):

4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 156588), m.p. 165-166°C.

10 Calcd. for $\text{C}_{10}\text{H}_8\text{Cl}_2\text{O}_3$: C 48.63 ; H 3.26 ; Cl 28.74

Found : 48.71 ; 3.38 ; 27.98

MS (FAB $^+$) m/z: 245 (M-H) $^+$.

^1H NMR (200 MHz; d_6 -DMSO), ppm : 2.57 (2H, t); 3.23 (2H, t); 7.79 (1H, d); 7.92 (1H, dd); 8.18 (1H, s); 12.10 (1H, broad

15 s);

4-oxo-4-(3'-chlorophenyl)butanoic acid; and

4-oxo-4-(3'-fluorophenyl)butanoic acid.

20 **Example 10**

(R,S)-3-Methyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 161243)

- 3-Methyl-4-oxo-4-(3',4'-dichlorophenyl)-2-butenic acid was prepared as below described. A well stirred mixture of 3'-chlorophenyl-1-propanone (12.9 g, 0.05 mol) and glyoxylic acid monohydrate (4.6 g, 0.05 mol) was heated for 22 hours at 120°C under vacuum (0.1 mmHg), in order to remove the water formed during the reaction. The resulting dark red residue was dissolved in diethyl ether and the organic phase extracted with saturated NaHCO_3 solution, the combined alkaline extracts were whashed with diethyl ether, to the stirred and cooled aqueous solution, 37% HCl was added dropwise until the pH of the solution was 1. The resulting suspension was extracted with
- 25
- 30

ethyl acetate, and the combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated in vacuo to provide the crude product. Column chromatography (SiO_2 ; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) afforded the pure 3-Methyl-4-oxo-4-(3',4'-dichlorophenyl)-2-butenic acid, (8.4 g, 65%), colorless plates, mp. 143-144°C (Toluene).

MS, EI (m/z) : 258.0 (M)⁺; 223.0 (M-Cl)⁺; 205.0 (M-Cl-H₂O)⁺; 172.9 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 2.20 (3H, s); 6.08 (1H, s); 7.63 (1H, dd); 7.75 (1H, d); 7.90 (1H, d).

To a solution of 3-Methyl-4-oxo-4-(3',4'-dichlorophenyl)-2-butenic acid (0.850 g, 3.3 mmol) in ethyl acetate (80 mL), Pd/C 5% (200 mg) is added, and the resulting suspension was hydrogenated at 30 p.s.i for 30 min. at room temperature. The catalyst was filtered and the filtrate concentrated in vacuo to an oily residue. Column chromatography (SiO_2 ; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4) afforded the pure 3-Methyl-4-oxo-(3',4'-dichlorophenyl) butanoic acid (0.625 g, 73%), colorless needles, mp. 124-126°C.

Calcd. for C₁₁H₁₀Cl₂O₃ : C 50.60 ; H 3.86 ; Cl 27.16
found : 51.19 ; 3.98 ; 26.97

MS, EI (m/z) : 260.0 (M)⁺; 172.9 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 1.08 (3H, d); 2.38-2.79 (2H, m); 3.80 (1H, m); 7.78 (1H, d); 7.89 (1H, dd); 8.12 (1H, d); 12.30 (1H, broad s).

25

Analogously, starting from the appropriate compound of formula (IV), the following compound can be obtained:

(R,S)-3-Phenyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 167541).

30

The corresponding 3-Phenyl-4-oxo-4-(3',4'-dichlorophenyl)-2-butenic acid was obtained as above described, m.p. 101-103°C, starting from 1-(3',4'-dichlorophenyl)-2-phenyl ethanone.

Reduction of the unsaturated acid afforded the corresponding
5 butanoic acid (PNU 167541): colorless prisms, mp. 147-148°C.

Calcd. for $C_{16}H_{12}Cl_2O_3$: C 59.49 ; H 3.74 ; Cl 22.95

found : 59.46 ; 3.79 ; 22.96

1H NMR (200 MHz; d_6 -DMSO), ppm : 2.74 (1H, dd); 3.42 (1H, dd);
4.93 (1H, m); 7.21 (5H, m); 7.43 (1H, d); 7.88 (1H, dd); 8.12 (1H,
10 d).

(R,S)-3-Benzyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid
can be analogously obtained starting from 1-(3',4'-
dichlorophenyl)-3-phenyl propanone.

15

Example 11

Methyl (R,S)-2-Phenyl-4-oxo-4-(3',4'-dichlorophenyl)butanoate (PNU 166928)

20 To a stirred suspension of cuprous bromide dimethylsulfide complex (Fluka) (0.870 g, 4.2 mmol) in dry THF (50 mL), 1.8 M phenylmagnesium bromide solution in THF (mL 7.0, 12.6 mmol) was added dropwise over 10 min., under dry nitrogen atmosphere, at 0°C. The resulting solution was cooled at -30°C and Methyl (E)-
25 4-oxo-4-(3',4'-dichlorophenyl) butanoate (2.2 g, 8.5 mmol) dissolved in dry THF (120 mL), was slowly added dropwise, maintaining the reaction temperature below -25°C. During the addition the color of the reaction mixture turned from deep green to cream. Completed the addition the resulting solution
30 was allowed to warm to room temperature and the reaction was quenched in 20% NH_4Cl /ice. The resulting slurry was extracted with diethyl ether and the combined organic extracts were washed with brine dried and concentrated under reduced pressure to a

pale yellow oil. Column chromatography (SiO_2 ; hexane/diethyl ether, 90:10) led to the pure methylester (2.2 g; 78%) as a colorless oil, which crystallized on treatment with diisopropyl ether/hexane, colorless plates, mp. 81-82°C.

5 Calcd. for $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_3$: C 60.53 ; H 4.15 ; Cl 21.07

found : 60.92 ; 4.33 ; 21.08

MS, EI (m/z) : 336.0 (M)⁺; 304 (M-CH₃OH)⁺; 173.0 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 3.40 (1H, dd); 3.58 (3H, s);
3.96 (1H, dd); 4.18 (1H, dd); 7.23-7.40 (5H, m); 7.78 (1H, d);

10 7.89 (1H, dd); 8.12 (1H, d).

Analogously, Methyl (R,S)-2-Benzyl-4-oxo-4-(3',4'-dichlorophenyl)butanoate (PNU 167531) was prepared using benzyl magnesium bromide instead of phenyl magnesium bromide.

15 Colorless prisms, mp. 72-73°C.

Calcd. for $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{O}_3$: C 61.55 ; H 4.59 ; Cl 20.19

found : 61.92 ; 4.73 ; 20.02

MS, EI (m/z) : 350.0 (M)⁺; 318.0 (M-CH₃OH)⁺; 173.0 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 2.80-2.93 (1H, m); 2.91 (1H, d);
20 3.13 (1H, dd); 3.37 (1H, m); 3.39 (1H, d); 3.65 (3H, s);
7.09-7.24 (5H, m); 7.72 (1H, d); 7.78 (1H, dd); 7.97 (1H, d).

Example 12

(R,S)-2-Phenyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU

25 167533)

To a solution of Methyl (R,S)-2-Phenyl-4-oxo-4-(3',4'-dichlorophenyl)butanoate (1.8 g, 5.3 mmol) in methanol (80 mL) cooled at 0°C, aqueous 1N sodium hydroxide (10.6 mL, 10.6 mmol) was added dropwise on stirring. The resulting reaction mixture
30 was stirred at 0°C 1 hour, then allowed to warm to room temperature and stirred further 3 hours. The most of the solvent was evaporated under reduced pressure and the residue diluted with water. The resulting solution was acidified with 37% HCl to

pH 2 and extracted with diethyl ether, the combined organic extracts were washed with brine dried and concentrated to a colorless solid (1.8 g). Recrystallization from diethyl ether afforded the pure acid (1.4 g, 83%), colorless needles, mp. 166-167°C.

Calcd. for $C_{16}H_{12}Cl_2O_3$: C 59.47 ; H 3.74 ; Cl 21.94

found : 59.47 ; 3.82 ; 21.64

MS, EI (m/z) : 322.0 (M)⁺; 304.0 (M-H₂O); 275.0 (M-COOH)⁺; 173.0 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 3.23 (1H, dd); 3.80-4.09 (2H, m); 7.10-7.2 (5H, m); 7.78 (1H, d); 7.94 (1H, dd); 8.22 (1H, d).

Analogously, (R,S)-2-Benzyl-4-oxo-4-(3',4'-dichlorophenyl)butanoic acid (PNU 167531) was prepared starting from Methyl (R,S)-2-Benzyl-4-oxo-4-(3',4'-dichlorophenyl)butanoate. Colorless prisms, mp. 147-148°C.

Calcd. for $C_{17}H_{14}Cl_2O_3$: C 60.55 ; H 4.18 ; Cl 21.03

found : 60.92 ; 4.32 ; 20.74

MS, EI (m/z) : 336.0 (M)⁺; 289.0 (M-COOH)⁺; 173.0 (C₆H₃Cl₂CO)⁺.

¹H NMR (200 MHz; d₆-DMSO), ppm : 2.80-3.94 (2H, m); 3.20-3.40 (3H, m); 7.10-7.15 (5H, m); 7.50 (1H, d); 7.67 (1H, dd); 7.97 (1H, d).

Example 13

Capsule, each weighing 0.23 g and containing 50 mg of the active substance can be prepared as follows:

Composition for 500 capsules:

4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid	25 g
Lactose	80 g
Corn starch	5 g
Magnesium stearate	5 g

This formulation can be encapsulated in two hard gelatin capsules of two pieces, each with each capsule weighing 0.23 g.

Example 14Intramuscular injection of 50 mg/ml

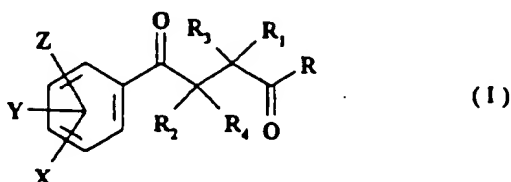
A pharmaceutical injectable composition can be manufactured
5 dissolving 50 g of 4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid
in sterile propyleneglycol (1000 ml) and sealed in 1-5 ml
ampoules.

Legend to Figure 1, which shows Kynurenine pathway

- 10 IDO : Indolamineoxygenase,
- KYN : kynurenine
- KYN-3-OHase : Kynurenine-3-hydroxylase
- KYN-3-OH : 3-hydroxy kynurenine
- KAT : Kynurenine amino transferase
- 15 3-OHAA : 3-hydroxy anthranilic acid
- KYNase : Kynureninase
- 3-HAO : 3-hydroxy anthranilic acid dioxygenase
- KYNA : Kynurenic acid
- QUIN : quinolinic acid
- 20 TDO : tryptophanedioxygenase

CLAIMS

1. A 4-phenyl-4-oxo-butanoic acid derivative of formula (I)
 5 either as single isomer or as a mixture of isomers



wherein

- 10 X, Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;

- R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in
 15 which each R₆ is, independently, hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, phenyl or benzyl;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, C₂-C₄ alkenyl, phenyl or benzyl, or

- 20 R₁ and R₃ or R₂ and R₄ together form a group =CHR₈ in which R₈ is hydrogen, a straight C₁-C₅ alkyl chain or phenyl;
 or a pharmaceutically acceptable salts thereof, for use in a method of treatment of the human or animal body by therapy.

2. A compound as claimed in claim 1, for use as kynurenine-3-
 25 hydroxylase inhibitor.

3. A compound as claimed in claim 2, for use in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-hydroxylase is needed.

4. A compound as claimed in claim 3 wherein the
 30 neurodegenerative disease comprises:

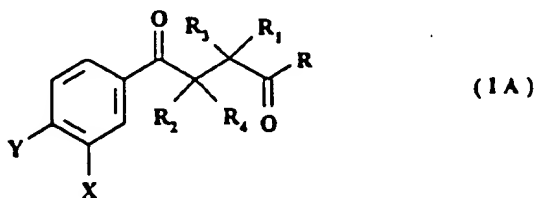
Huntington's chorea, Alzheimer's disease, dementia caused by
 acquired immunodeficiency syndrome (AIDS), infarctual dementia,
 cerebral ischemia, cerebral hypoxia, Parkinson's disease,
 epilepsy, head and spinal cord injury, amyotrophic lateral
 5 sclerosis, glaucoma\retinopathy, infections and inflammations of
 the brain.

5. Use of a compound as defined in claim 1 in the manufacture
 of a medicament for use as kynurenine-3-hydroxylase inhibitor.

6. Use according to claim 5 wherein the medicament is for use
 10 in the prevention and/or treatment of a neurodegenerative
 disease wherein the inhibition of the enzyme kynurenine-3-
 hydroxylase is needed.

7. Use according to claim 6 wherein the neurodegenerative
 disease comprises Huntington's chorea, Alzheimer's disease,
 15 dementia caused by acquired immunodeficiency syndrome (AIDS),
 infarctual dementia, cerebral ischemia, cerebral hypoxia,
 Parkinson's disease, epilepsy, head and spinal cord injury,
 amyotrophic lateral sclerosis, glaucoma retinopathy, infections
 and inflammations of the brain.

20 8. A 4-phenyl-4-oxo-butanoic acid derivative of formula (IA)
 either as single isomer or as a mixture of isomers



25 wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl,
 benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in
 which each of R₆ is hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄
 30 alkynyl, phenyl or benzyl;

R_1 , R_2 , R_3 and R_4 are, each independently, hydrogen, halogen, hydroxy, cyano, thiol, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkyl, C_2 - C_4 alkenyl, phenyl or benzyl, or

R_1 and R_3 or R_2 and R_4 together form a group $=CHR_5$ in which R_5 is hydrogen, a straight C_1 - C_5 alkyl chain or phenyl;
or a pharmaceutically acceptable salt thereof;

provided that:

- (i) when X and Y are both chlorine and R_1 , R_2 and R_4 are simultaneously hydrogen, R_3 is different from hydrogen, hydroxy, methoxy, ethylthio or isopropylthio; and
(ii) when X and Y are both fluorine, R_1 , R_2 , R_3 and R_4 are not simultaneously hydrogen.

9. A compound as claimed in claim 8 wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy or $-OR_5$ in which R_5 is C_1 - C_6 alkyl;

R_1 , R_2 , R_3 and R_4 are, each independently, hydrogen, halogen, cyano, hydroxy, thiol, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkyl, phenyl, benzyl or C_2 - C_4 alkenyl, or

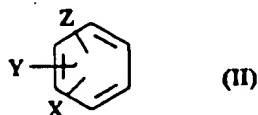
R_1 and R_3 or R_2 and R_4 together form a group $=CHR_5$ in which R_5 is hydrogen, a straight C_1 - C_5 alkyl or phenyl;
and the pharmaceutically acceptable salts thereof;
provided that:

- (i) when X and Y are both chlorine and R_1 , R_2 and R_4 are simultaneously hydrogen, R_3 is different from hydrogen, hydroxy, methoxy, ethylthio or isopropylthio; and
(ii) when X and Y are both fluorine, R_1 , R_2 , R_3 and R_4 are not simultaneously hydrogen.

10. A compound selected from:

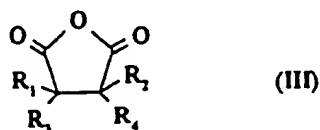
- 2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
2-methoxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
2-hydroxy-3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-hydroxy-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

- 2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-methyl-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 2-chloro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-chloro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 5 2-fluoro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-fluoro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
 2-thiomethyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-methyliden-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 2-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 10 2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
 15 (R,S)-methyl-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
 (R,S)-methyl-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
 and their pharmaceutically acceptable salts.
11. A process for preparing a compound of formula (I) as defined in claim 1 or (IA) as defined in claim 8 which comprises:
- 20 a) reacting a compound of formula (II)



wherein

- 25 X, Y and Z are, each independently, hydrogen, halogen, cyano, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;
 with a compound of formula (III)

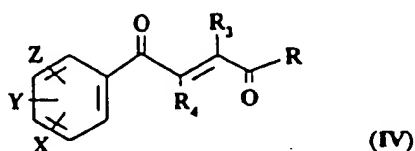


wherein

R_1 , R_2 , R_3 and R_4 are each independently, hydrogen, C_1 - C_6 alkyl, C_2 - C_4 alkenyl, phenyl or benzyl, or

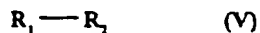
- 5 R_1 and R_3 or R_2 and R_4 together form a group $=CHR_5$ in which R_5 is hydrogen, a straight C_1 - C_3 alkyl chain or phenyl;
so obtaining a compound of formula (I) or (IA) wherein
 X , Y , Z , R_1 , R_2 , R_3 and R_4 are as defined above and R is hydroxy; or

- 10 b) reacting a compound of formula (IV)



wherein

- 15 X , Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C_1 - C_6 alkyl, phenyl, benzyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio;
 R is hydroxy or $-OR_5$ in which R_5 is C_1 - C_6 alkyl; and
 R_3 and R_4 are, each independently, hydrogen, halogen, C_1 - C_6 alkyl, phenyl or benzyl;
20 with a compound of formula (V)



- 25 wherein

- R_1 is hydrogen, halogen, hydroxy, sulfidryl C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkyl, phenyl or benzyl; and
 R_2 is hydrogen, halogen, hydroxy, an alkali metal or an alkaline-earth metal, e.g. magnesium; provided that when R_1
30 is sulfidryl or C_1 - C_6 alkylthio R_2 is not hydroxy or halogen;
so obtaining a compound of formula (I) or (IA) wherein

X, Y, Z, R₁, R₂, R₃ and R₄ are as defined above;
and, if desired,

- c) converting a compound of formula (I) or (IA) as obtained in step a) or b) above, into another compound of formula (I) or (IA) in which one or more of R₁, R₂, R₃ and R₄ has/have different meaning; and/or, if desired,
- d) converting a compound of formula (I) or (IA) as obtained in step a), b) or c) above, into another compound of formula (I) or (IA) wherein R is not hydroxy; or, if desired,
- 10 e) converting a compound of formula (I) or (IA) as obtained in step a), b) or c) above, into a pharmaceutically acceptable salt thereof or obtaining the free compound from the corresponding salt; and/or, if the compound of formula (I) or (IA) is obtained as a mixture of isomers,
- 15 f) obtaining a single isomer of a compound of formula (I) or (IA) as obtained in step a), b), c), d) or e) from the corresponding mixture of isomers.

12. A pharmaceutical composition which comprises as an active substance a compound as defined in claim 1 in association with a pharmaceutically acceptable carrier and/or diluent.

13. A pharmaceutical composition which comprises as an active substance a compound as defined in claim 8 in association with a pharmaceutically acceptable carrier and/or diluent.

14. A compound as claimed in claim 8, for use in a method of treatment of the human or animal body by therapy.

15. A compound as claimed in claim 14, for use as a kynurenine-3-hydroxylase inhibitor.

16. A compound as claimed in claim 15, for use in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-hydroxylase is needed.

17. A compound as claimed in claim 16 wherein the neurodegenerative disease comprises Huntington's chorea, Alzheimer's disease, dementia caused by acquired immunodeficiency

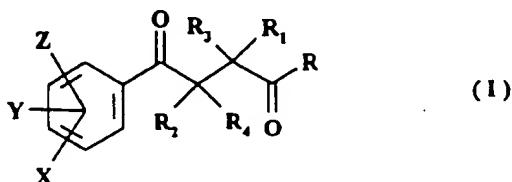
syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma retinopathy, infections and inflammations of the brain.

- 5 18. A pharmaceutical composition which comprises as an active substance a compound as defined in claim 1 in association with a pharmaceutically acceptable carrier and/or diluent, for use as kynurenine-3-hydroxylase inhibitor.

AMENDED CLAIMS

[received by the International Bureau on 10 April 1997 (10.04.97);
original claims 1-18 replaced by amended claims 1-17 (6 pages)]

1. A 4-phenyl-4-oxo-butanoic acid compound of formula (I)
5 either as single isomer or as a mixture of isomers thereof



wherein

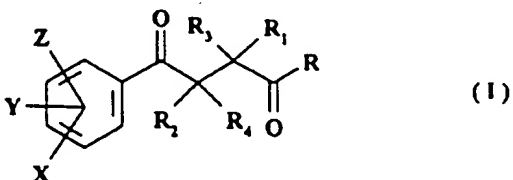
- 10 X, Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₆ alkoxy or C₁-C₆ alkylthio;

- R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in
15 which each R₆ is, independently, hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, phenyl or benzyl;

R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, C₂-C₄ alkenyl, phenyl or benzyl, or

- 20 R₁ and R₃ or R₂ and R₄ together form a group =CHR₆ in which R₆ is hydrogen, a straight C₁-C₃ alkyl chain or phenyl;
or a pharmaceutically acceptable salts thereof; and wherein when, at the same time, X is hydrogen, halogen or phenyl; Y is hydrogen or C₁-C₆ alkoxy; R₁ and R₃ together form a =CH₂ group and
25 R is hydroxy or C₁-C₆ alkoxy, then at least one of Z, R₂ and R₄ is other than hydrogen; wherein when, at the same time, X is hydrogen, halogen, C₁-C₆ alkyl or C₁-C₆ alkoxy; Y is phenyl; R₃ is methyl and Z, R₁, R₂ and R₄ are hydrogen, then R is other than hydroxy; and wherein when, at the same time, Y is iso-propyl or
30 tertiary-butyl; X is chlorine or nitro; R is hydroxy, C₁-C₆

- alkoxy or $-N(R_6)_2$ in which each R_6 is hydrogen or C_1-C_6 alkyl, then at least one of R_1 , R_2 , R_3 , R_4 and Z is other than hydrogen; for use in a method of treatment of the human or animal body by therapy.
2. A compound as claimed in claim 1, for use as kynurenine-3-hydroxylase inhibitor.
3. A compound as claimed in claim 1, for use in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-hydroxylase is needed.
4. A compound according to claim 3 wherein the neurodegenerative disease comprises:
Huntington's chorea, Alzheimer's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma\retinopathy, infections and inflammations of the brain.
5. A pharmaceutical composition which comprises as an active substance a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier and/or diluent.
6. Use of a compound of formula (I) either as single isomer or as a mixture of isomers thereof



wherein

X , Y and Z are, each independently, hydrogen, halogen, cyano, nitro, C_1-C_6 alkyl, phenyl, benzyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_6 alkoxy or C_1-C_6 alkylthio;

R is hydroxy; $-OR_5$ in which R_5 is C_1-C_6 alkyl, phenyl, benzyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl; $-N(R_6)_2$ or $-N(R_6)OR_6$ in which each R_6 is, independently, hydrogen, C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl or benzyl;

- 5 R_1 , R_2 , R_3 and R_4 are, each independently, hydrogen, halogen, hydroxy, thiol, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkyl, C_2-C_4 alkenyl, phenyl or benzyl, or

R_1 and R_3 or R_2 and R_4 together form a group $=CHR_8$ in which R_8 is hydrogen, a straight C_1-C_5 alkyl chain or phenyl;

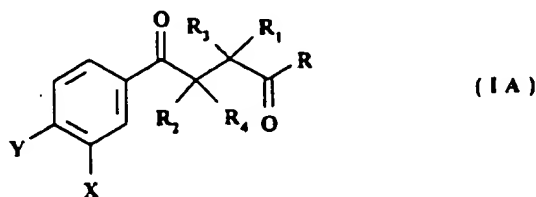
- 10 or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for use as kynurenine-3-hydroxylase inhibitor.

7. Use according to claim 6 wherein the medicament is for use in the prevention and/or treatment of a neurodegenerative disease wherein the inhibition of the enzyme kynurenine-3-
15 hydroxylase is needed.

8. Use according to claim 7 wherein the neurodegenerative disease comprises Huntington's chorea, Alzheimer's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia,
20 Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma retinopathy, infections and inflammations of the brain.

9. A 4-phenyl-4-oxo-butanoic acid compound of formula (IA) either as single isomer or as a mixture of isomers thereof

25



wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy; -OR₅ in which R₅ is C₁-C₆ alkyl, phenyl, benzyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl; -N(R₆)₂ or -N(R₆)OR₆ in which each of R₆ is hydrogen, C₁-C₆ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, phenyl or benzyl;

5 R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, hydroxy, cyano, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, C₂-C₄ alkenyl, phenyl or benzyl, or

R₁ and R₃ or R₂ and R₄ together form a group =CHR₈ in which R₈ is hydrogen, a straight C₁-C₆ alkyl chain or phenyl;

10 or a pharmaceutically acceptable salt thereof;

provided that:

- (i) when X and Y are both chlorine and R₁, R₂ and R₄ are simultaneously hydrogen, R₃ is different from hydrogen, hydroxy, methoxy, ethylthio or isopropylthio; and
- 15 (ii) when X and Y are both fluorine, R₁, R₂, R₃ and R₄ are not simultaneously hydrogen.

10. A compound as claimed in claim 9 wherein

X and Y are, each independently, fluorine or chlorine;

R is hydroxy or -OR₅ in which R₅ is C₁-C₆ alkyl;

20 R₁, R₂, R₃ and R₄ are, each independently, hydrogen, halogen, cyano, hydroxy, thiol, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkyl, phenyl, benzyl or C₂-C₄ alkenyl, or

R₁ and R₃ or R₂ and R₄ together form a group =CHR₈ in which R₈ is hydrogen, a straight C₁-C₆ alkyl or phenyl; or a

25 pharmaceutically acceptable salt thereof.

11. A compound selected from:

2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;

2-methoxy-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;

2-hydroxy-3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

30 2-hydroxy-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;

2-methyl-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;

- 2-chloro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-chloro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
2-fluoro-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-fluoro-4-(3',4'-difluorophenyl)-4-oxo-butanoic acid;
5 2-thiomethyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-methyliden-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
10 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoic acid;
(R,S)-methyl-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
(R,S)-methyl-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-butanoate;
15 either as a single isomer or as a mixture thereof or a
pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition which comprises as an active
substance a compound as defined in claim 9, or a
pharmaceutically acceptable salt thereof, in association with a
20 pharmaceutically acceptable carrier and/or diluent.

13. A compound as claimed in claim 9, or a pharmaceutically
acceptable salt thereof, for use in a method of treatment of the
human or animal body by therapy.

14. A compound as claimed in claim 9, or a pharmaceutically
25 acceptable salt thereof, for use as a kynurenine-3-hydroxylase
inhibitor.

15. A compound as claimed in claim 9, or a pharmaceutically
acceptable salt thereof for use, in the prevention and/or
treatment of a neurodegenerative disease wherein the inhibition
30 of the enzyme kynurenine-3-hydroxylase is needed.

16. A compound as claimed in claim 15 wherein the
neurodegenerative disease comprises Huntington's chorea,
Alzheimer's disease, dementia caused by acquired immunodeficiency

- syndrome (AIDS), infarctual dementia, cerebral ischemia, cerebral hypoxia, Parkinson's disease, epilepsy, head and spinal cord injury, amyotrophic lateral sclerosis, glaucoma retinopathy, infections and inflammations of the brain.
- 5 17. A method of treating a patient in need of a kynurenine-3-hydroxylase inhibitor, the method comprising administering to said patient an effective amount of a compound of formula (I) or of formula (IA), according to claims 6 and 9, respectively, or a pharmaceutically acceptable salt thereof.

STATEMENT UNDER ARTICLE 19

The claims have been amended in the light of the prior art cited in the International Search Report.

The claims have been also submitted to some minor editorial amendments.

In particular, the provisos at the end of amended claim 10 (original claim 9) have been deleted, as being redundant in view of dependency on claim 9.

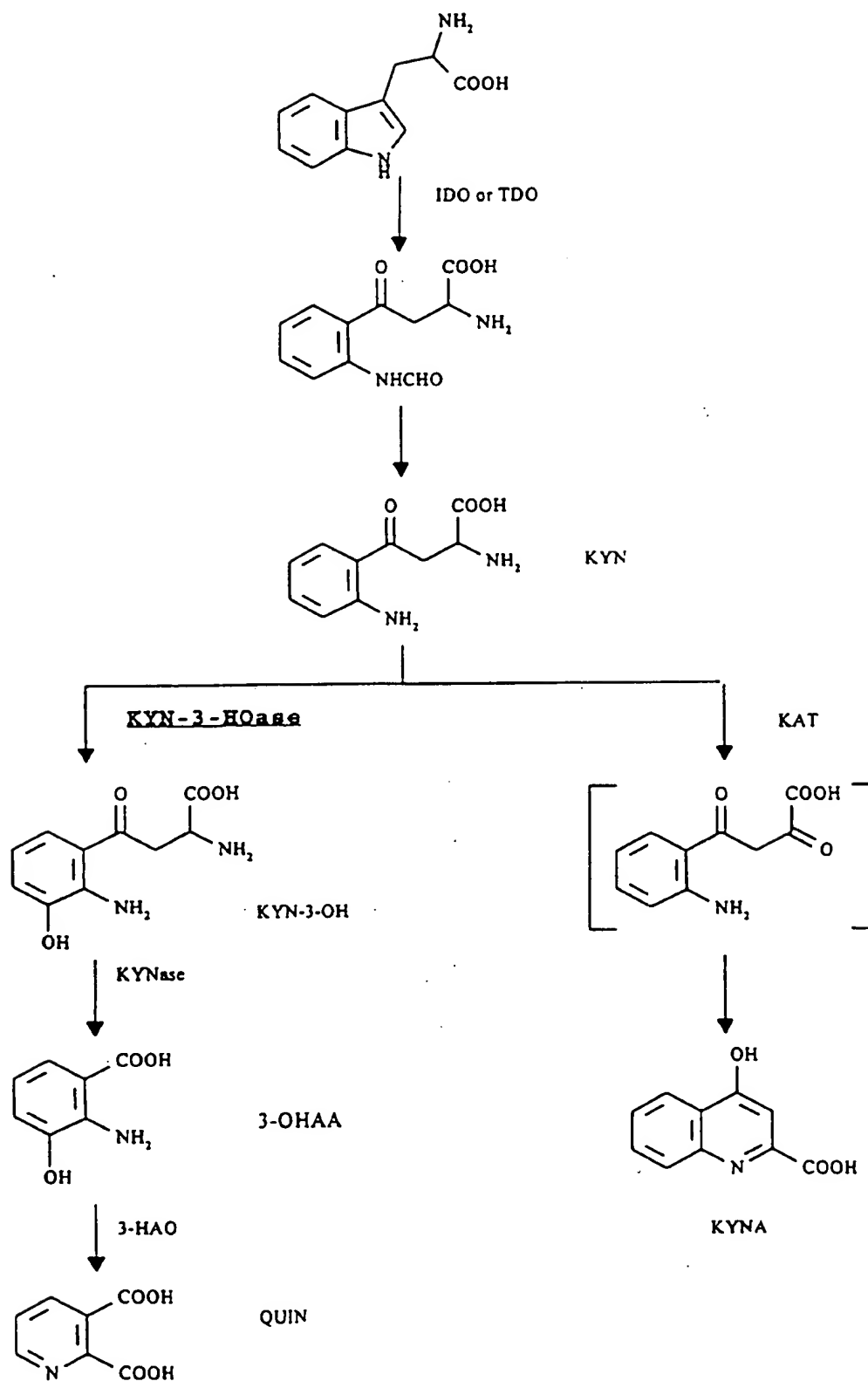
Original process claim 11 has been deleted.

New claim 17 finds its counterpart on page 20, lines 14-16 of the specification.

In view of the above it will be appreciated that the amendments to the claims do not go beyond the disclosure of the application as filed.

1/1

Figure 1



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/04518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C59/90 A61K31/19 C07C59/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,1 498 903 (PIERRE FABRE S.A.) 25 January 1978 ENTIRE DOCUMENT. ---	1-7,12, 18
X	GB,A,1 565 616 (PIERRE FABRE S.A.) 23 April 1980 ENTIRE DOCUMENT. ---	1-7,12, 18
X	FR,A,2 503 140 (PIERRE FABRE S.A.) 8 October 1982 ENTIRE DOCUMENT. ---	1-7,12, 18
X	GB,A,1 068 751 (THE UPJOHN COMPANY) 10 May 1967 see page 3, line 7 - line 10 see page 11, line 3 - line 21 --- -/--	1-7,12, 18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

3 February 1997

Date of mailing of the international search report

1 0. 02 97

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Fax (+ 31-70) 340-3016

Authorized officer

Klag, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/04518

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,3 876 800 (KRAUSZ ET AL.) 8 April 1975 ENTIRE DOCUMENT. -----	1-7,12, 18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/04518

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
As the drafting of the claims is not clear and concise and encompasses such enormous amount of products, a complete search is not possible on economic grounds. So the search has been based on the examples.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/04518

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		FR-A- 2300551	10-09-76
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		NL-A- 7006851	16-11-70
		SE-B- 379039	22-09-75